A 25-year follow-up of patients admitted to methadone treatment for the first time: Mortality and gender differences

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Abstract

Keywords: Mortality Heroin addiction Methadone Maintenance Therapy Gender

Introduction: We conducted a follow-up study to evaluate the outcome of a heroin-dependent population 25 years after their first enrollment in methadone maintenance treatment (MMT). We assessed mortality in the sample plus actual drug use, treatment, and medical factors associated with drug dependence, focusing on possible gender differences.

Methods: Prospective follow-up study of 214 heroin-dependent patients consecutively admitted for MMT between 1980 and 1984 in the Asturias Public Health Service. The standardized mortality ratio (SMR) and 95% confidence interval (CI) were calculated. An ad-hoc protocol on drug misuse and treatment, drug-related morbidity and Clinical Global Impression (CGI) scores were assessed in the survivors’ sample.

Results: Information was received on 159 subjects, 106 of whom were deceased. Men accounted for 76.2% of the study cohort. Over the 25-year follow-up period, the SMR was 22.51 (95% CI=22.37–22.64). In the survivors sample, 39.6% were still enrolled in MMT; human immunodeficiency virus (HIV) was diagnosed in 47.2% and hepatitis B/C in 81.1%; current heroin use was reported by 22.6%. There were no gender differences in mortality or HIV and hepatitis B/C status. None of the female survivors were using heroin at the 25-year follow-up compared with 31.1% of males.

Conclusions: This study confirms the high mortality of heroin addicts even after enrollment in MMT. Severity of the addiction in terms of mortality was similar in both genders. Women who survived the 25-year follow-up were more likely to have stopped using heroin than men.

1. Introduction

Heroin addiction has often been characterized as a chronic relapsing condition, and for many addicts, it is a persistent, long-term affliction with severe consequences, particularly in terms of premature mortality and high morbidity (Hser, Hoffman, Grella, & Anglin, 2001). One of the principal treatments for heroin dependence in many countries is methadone maintenance treatment (MMT) (Hall, Lyskøy, & Degenhardt, 2000) with an estimated 1 million individuals receiving MMT worldwide (Kleber, 2008).

Numerous studies have demonstrated the effectiveness of MMT for reducing illicit opioid use, morbidity and mortality, risk of human immunodeficiency virus (HIV) infection, and illegal activities, and for improving overall functioning (Kleber, 2008). Patients in MMT have a 1-year mortality rate of 1% (Zanis & Woody, 1998) while a number of studies have suggested that the annual death rate of young adult drug abusers lies at around 2% to 8% per year (Haastrup & Jepsen, 1988; Oppenheimer, Tobutt, Taylor, & Andrew, 1994; Ravndal & Vlagum, 1998; Segest, Mygind, & Bay, 1990; Zanis & Woody, 1998). The benefits of long-term MMT are borne out by the data (National Institutes of Health, 1997). In randomized controlled trials and controlled observational studies, MMT has been shown to result in substantial reductions in illicit opioid use and criminal activity (Ward, Mattick, & Hall, 1998) and to substantially reduce opioid overdose deaths while individuals are enrolled in MMT (Caplehorn, Dalton, Cluff, & Petrenas, 1994; Caplehorn, Dalton, Haldar, Petrenas, & Nisbet, 1996; Gearing & Schweitzer, 1974; Zador, Sunjic, & Basili,
Although a considerable number of deaths still occur in patients on maintenance treatment, including many taking methadone (Heinemann, Iwersen-Bergmann, Stein, Schmoldt, & Püschel, 2000; Mattick & Degenhardt, 2003). Although MMT has been lifesaving for thousands of individuals, it is not a panacea. High levels of psychopathology remain. Abuse of cocaine and benzodiazepines and disruptive behavior are problems in many programs. Many patients do not change their behavior even when services are available (Kleber, 2008).

Generally, transition to abstinence is highest in the first few years that substance abusers are treated, but few become abstinent after the first few years (Haastrup & Jepsen, 1988; Hser et al., 2001; Hubbard, Caddock, & Anderson, 2003). Even patients receiving maintenance for long periods with substantial lifestyle changes often relapse after leaving treatment, and death rates are much higher than for individuals who remain in treatment. For many patients, therefore, years or even lifetime maintenance may be needed (Kleber, 2008).

Relatively little is known about long-term recovery processes among addicts who do achieve and maintain abstinence, as there are few long-term follow-up studies on this type of patients (see Table 1). This might be related to the difficulty of tracking substance abusers in longitudinal research (Jimenez et al., 2000; Walton, Ramathan, & Reischl, 1998).

Although drug overdose is the leading cause of death in most long-term follow-up studies on opioid dependence (Bauer et al., 2008; Goldstein & Herrera, 1995; Haastrup & Jepsen, 1988; Hall et al., 2000; Hser et al., 2001; Nehkant, Rathod, Addenbrooke, & Rosenbach, 2005; Oppenheimer et al., 1994), somatic comorbidities, such as HIV infection, were also associated with an increased mortality rate prior to the introduction of potent antiretroviral therapies in the mid-1990s (Muga et al., 2000). AIDS is a leading cause of death among injection drug users, and serious infections resulting in pneumonia, endocarditis, and sepsis are also responsible for high death rates among this subpopulation (Tyndall et al., 2001). Additionally, hepatitis C infections and nonalcoholic liver disease have been shown to negatively influence death rates (Appel, Joseph, & Richman, 2000).

The excess mortality over the life-span of drug abusers is of interest, because it implies the need for services over the life course, over and above the need for treatment services that show effectiveness in the short term (Fridell & Hesse, 2006).

The recent focus on drug abuse in women has brought attention to numerous differences between women and men (Lynch, Roth, & Carroll, 2002). Sex differences are present for all phases of drug abuse (initiation, escalation of use, addiction, and relapse following abstinence). Females begin regularly self-administering illicit and licit drugs of abuse at lower doses than do males, use escalating more rapidly to addiction, and females are at greater risk for relapse following abstinence (Becker & Hu, 2008). Clinical studies report outstanding differences with regard to substance misuse patterns, social support and evolution of the treatment according to the gender (either male or female). Men have better prognosis than women in the population studied. These differences seem to be due to the sociocultural contents of the gender concept (Ochoa, Madoz-Gúrpide, & Salvador, 2008).

Recent evidence suggests that the progression to dependence and abuse may differ between women and men; thus, different prevention and treatment strategies may be required. (Lynch et al., 2002). These gender differences in addictive behaviors have been explained by sociocultural as well as biological factors (Becker & Hu, 2008; Lynch et al., 2002).

Despite the evidence of gender differences in drug dependence, there is a lack of data from long-term follow-up studies concerning possible gender differences in death/survival rates. The few existing data suggest a higher mortality rate among men (Bauer et al., 2008; Coffin et al., 2003; Fridell & Hesse, 2006; Hickman et al., 2003).

The aim of our work is to evaluate the outcome of a heroin-dependent population 25 years after their first enrollment in MMT, focusing on gender differences. More specifically, we evaluate excess mortality by gender, plus current drug misuse and treatment, drug-related morbidity, and clinical global impression in the survivors.

## 2. Material and methods

### 2.1. Participants and setting

The study was conducted prospectively on a sample of 214 heroin-dependent patients consecutively admitted for MMT between 1980 and 1984 to different health facilities in the Asturias Public Health Service. They were the first patients to be enrolled in MMT in Asturias. The first interview took place at the time of enrollment in MMT. Data were collected by means of an ad-hoc protocol on drug dependence, including sociodemographic, clinical, family, job, and legal data. All subjects who presented for treatment were entered in the sample even if they left treatment prematurely.

### 2.2. Follow-up procedure

At the 15-year follow-up, patients were contacted by telephone. Data were collected by telephone interviews and/or review of medical records. The main findings from the 15-year follow-up are reported elsewhere (Jimenez et al., 2000).

The 25-year follow-up is the main subject of the present work. Prior to the assessment, we have made an extensive effort to locate the patients. Patients were invited to participate in the study in a telephone interview by members of the research team or in a personal interview by their regular health care provider.

Assessment interviews were done by a trained research psychologist. Personal interviews were preferred for the assessment, but telephone

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Country</th>
<th>Duration of follow-up (years)</th>
<th>Deaths%</th>
<th>Sample size and derivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauer et al. (2008)</td>
<td>Austria</td>
<td>5</td>
<td>25.4</td>
<td>269 opioid-dependents enrolled in MMT</td>
</tr>
<tr>
<td>Sanchez-Carbonell and Seus (2000)</td>
<td>Spain</td>
<td>10.5</td>
<td>30</td>
<td>138 heroin addicts admitted for the first time to EMETYST Project</td>
</tr>
<tr>
<td>Fridell and Hesse (2006)</td>
<td>Sweden</td>
<td>15</td>
<td>24</td>
<td>125 drug abusers admitted for detoxification at Santé Lars Hospital</td>
</tr>
<tr>
<td>Davstad et al. (2009)</td>
<td>Sweden</td>
<td>18</td>
<td>45</td>
<td>157 heroin-dependent subjects admitted for the first time to MMT in Stockholm</td>
</tr>
<tr>
<td>Vaillant (1973)</td>
<td>USA</td>
<td>20</td>
<td>23</td>
<td>100 people with narcotic addiction admitted to Lexington Hospital, NY</td>
</tr>
<tr>
<td>Oppenheimer et al. (1994)</td>
<td>UK</td>
<td>22</td>
<td>34</td>
<td>128 patients from 13 drug dependency clinics in London</td>
</tr>
<tr>
<td>Jimenez-Treviño et al. (present study)</td>
<td>Spain</td>
<td>25</td>
<td>49.5</td>
<td>214 heroin dependents admitted for the first time to MMT</td>
</tr>
<tr>
<td>Hser et al. (2001)</td>
<td>USA</td>
<td>33</td>
<td>48.9</td>
<td>581 white men admitted to California Drug Addiction Program</td>
</tr>
<tr>
<td>Nehkant et al. (2005)</td>
<td>UK</td>
<td>33</td>
<td>22</td>
<td>86 heroin dependents seen for therapeutic intervention</td>
</tr>
<tr>
<td>Stenbackas et al. (2010)</td>
<td>Sweden</td>
<td>37</td>
<td>50.4</td>
<td>1705 substance abusers identified through medical records in Stockholm</td>
</tr>
</tbody>
</table>

MMT = methadone maintenance treatment.
interviews were also accepted. Additional data was obtained from medical records or direct relatives.

Overall, 55 subjects (25.7%) could not be located. Information was, therefore, received regarding 159 subjects (74.3%), of whom 28 (13.1%) refused an interview and 106 (49.5%) were deceased. In total, 25 (11.7%) subjects were interviewed.

2.3. Number of deaths

We received information about the number of deaths from the Spanish Ministry of Health death register. Information on cause of death was not provided by the Ministry of Health and was collected by personal interview of direct relatives or by research of medical records, resulting in a loss of data. Information concerning the HIV status of the patients was obtained from medical records.

2.4. Measurements

An ad hoc protocol was used to collect data on the use of addiction treatment resources. Actual drug misuse was assessed by personal interview. Information concerning the HIV and HVB/C status of the patients was obtained by personal interview and medical records. Severity of illness was assessed by trained psychologists after a clinical interview using Clinical Global Impression (CGI) scale (Guy, 1976).

2.5. Statistical analyses

Our aim was to determine whether the study sample of heroin-dependent patients had a survival rate comparable to the demographically matched general population, according to the 2009 results provided by Spain’s National Statistics Institute (Instituto Nacional de Estadística, 2010). This hypothesis was tested using the procedure described by Finkelstein, Muzikansky, & Schoenfeld (2003). The standardized mortality ratio (SMR) and 95% confidence interval (CI) were calculated using the expected number of deaths in the sample, according to demographic statistics for the overall population. The null hypothesis was tested using a one-sample log-rank test. Additionally, Kaplan–Meier curves were constructed, which showed the expected and observed results. In order to assess the annual death rate for each year of age during follow-up, we used the convention proposition by Finkelstein et al. (2003) that both diagnosis and end of follow-up occur on a patient’s birthday. All calculations concerning SMR were performed using R software version 2.12.0 (R Development Core Team, 2009). All other calculations were done using SPSS 15.0 for Windows. The level of statistical significance was set at 0.05. Mean comparisons between two groups were performed using the t test for normally distributed independent samples. Nonparametric tests were used if necessary. When comparing categorical data, chi-square ($\chi^2$) tests were used.

2.6. Ethics

The study was conducted subject to and in compliance with Spanish national legislation. It was conducted according to the provisions of the World Medical Association Declaration of Helsinki (World Medical Association, 1989) and received institutional approval from the Clinical Research Ethic Committee of Asturias.

3. Results

3.1. Baseline versus follow-up samples

Demographic and clinical characteristics of survivors ($n=53$) compared with baseline data are shown in Table 2.

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=214)</th>
<th>15 years (n=82)</th>
<th>25 years (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD)</td>
<td>26.05 (8.57)</td>
<td>25.29 (4.30)</td>
<td>39.03 (7.88)</td>
</tr>
<tr>
<td>1st heroin (SD)</td>
<td>18.02 (1.77)</td>
<td>19.79 (2.31)</td>
<td>20.0 (10.06)</td>
</tr>
<tr>
<td>HIV+</td>
<td>75.6% (24.4%)</td>
<td>24.4% (77.4%)</td>
<td>49.81 (22.6%)</td>
</tr>
<tr>
<td>HVB/C+</td>
<td>78.8% (37.5%)</td>
<td>46.5% (25.7%)</td>
<td>78.6% (53.8%)</td>
</tr>
<tr>
<td>Current MMT</td>
<td>100% (100%)</td>
<td><em>51.1%</em> (20.0%)</td>
<td><em>32.5%</em> (0%)</td>
</tr>
</tbody>
</table>

*Men vs. women difference $p<0.05$.

3.2. HIV/Hepatitis B status

47.2% ($n=25$) of the survivors had an HIV diagnosis at the 25-year follow-up compared with 35.6% ($n=29$) at the 15-year follow-up. Hepatitis B or C was diagnosed in 81.1% ($n=43$) at the 25-year follow-up compared with 80.0% ($n=66$) at the 15-year follow-up.

There were no gender differences in either HIV ($\chi^2=0.087$, $p=0.497$) or hepatitis B/C ($\chi^2=2.245$, $p=0.137$) status.

3.3. Past and current use of heroin

The entire sample used heroin at the start of the study. The mean age of first heroin use was 18.39 (SD = 2.995). Women started using heroin 1.77 years later than men ($t$ test = $-2.008$, $p=0.049$). There was no difference between the survivors and the deceased samples in mean age of first heroin use ($t$ test = $-1.185$, $p=0.241$).

At the 25-year follow-up, 22.6% of survivors reported current heroin use compared with 39.7% at the 15-year follow-up. None of the female survivors were using heroin at the 25-year follow-up compared with 31.1% of male survivors (Fisher’s exact test, $p=0.038$).

3.4. Current methadone maintenance therapy

The entire sample started MMT at the beginning of the study. At the 15-year follow-up, 60.4% of the survivors were still enrolled in MMT, and at the 25-year follow-up, only 39.6% of the survivors were enrolled in MMT. There were no gender differences in current MMT enrollment in the survivors sample ($\chi^2=0.555$, $p=0.345$).

3.5. CGI score

The mean CGI score of the sample was 3.76 (SD = 1.71). There were no gender differences in CGI score ($t$ test = $-1.129$, $p=0.271$). Patients still enrolled in MMT had lower mean CGI scores than people currently out of MMT [2.92 (SD = 1.78) vs. 4.54 (SD = 1.3); $t$ test = $-2.640$, $p=0.015$].
3.6 Mortality

A total of 106 individuals (83 men, 23 women) had died by December 31, 2009. The first SMR calculations were performed using this sample size. The mean age of deceased patients was 37.81 years (SD = 9.30); the youngest person died at the age of 24 and the oldest at the age of 84 years. There was no difference in mean age of death between men and women (t = 0.320, p = 0.750).

The expected death toll for the general population in the follow-up period analyzed was 5.62 in comparison with 106 deaths observed in the heroin-dependent population. Over the 25-year follow-up period, the SMR in the deceased group (n = 106) was 22.51 (95% CI = 22.37–22.64) (Fig. 1).

After repeating the analysis by gender, we observed the following results: 83 deaths were observed in the men of the heroin-dependent population in comparison to the expected death toll for the general population of 4.96. Over the 25-year follow-up period, the SMR in the deceased group (n = 83) was 16.73 (95% CI = 16.62–16.85).

Twenty-three deaths were observed in the women of the heroin-dependent population in comparison to the expected death toll for the general population of 0.66. Over the 25-year follow-up period, the SMR in the deceased group (n = 23) was 32.86 (95% CI = 32.43–33.29). There were no differences in Kaplan–Meier curves by gender (p = 0.0743) (Fig. 2).

Detailed information concerning the cause of death was obtained only for 41 (38.7%) of these subjects using medical records and information provided by direct relatives. Causes of death by gender are shown in Table 3. Statistical tests were not applied due to lack of data and excess of missing/unknown causes.

4 Discussion

4.1 Mortality

This study confirms the high mortality of heroin addicts even after enrollment in MMT.

Our data (death rate of 49.5% after 25 years) agree with a number of studies in non-MMT patients suggesting that the annual death rate of young adult drug abusers lies around 2% per year (Haastrup & Jepsen, 1988; Oppenheimer et al., 1994; Ravndal & Vaglum, 1998; Segest et al., 1990), although data from other long-term follow-up studies show great variability (See Table 3).

It should be noted that comparing these types of studies is difficult because of the use of different study groups, methods, and calculations as well as different sample sizes, countries of origin, and length of follow-up periods.

We used the SMR as a more accurate way to compare death figures. After a mean follow-up period of 25 years, the SMR of 22.51 in our cohort was comparable to 28.5 found by Sanchez-Carbonell and Seus (2000); 22 found by Frischer, Goldberg, Rahman, and Berney (1997); 29.13 found by Bauer et al. (2008), but higher 10.1 found by Perucci, Davoli, Rapiti, Forastiere, and Abeni (1991); 9.7 found by Rehm et al. (2005); and 12.85 found by Quaglio et al. (2001). A study by Risser et al. (2001) found that SMR dramatically increased in an untreated population – 48.8 vs. 12.1 in patients undergoing opioid maintenance therapy – but this was found in a much shorter study period of 3 years. Therefore, SMR data should be interpreted cautiously, as follow-up after a longer period of time may elevate the number of deaths in treated populations due to long-term morbidity associated with HIV and/or HBV.

Regarding the influence of gender, this study disagrees in part with the higher mortality rate among men found in other studies (Bauer et al., 2008; Coffin et al., 2003; Hickman et al., 2003; Stenbacka, Leifman, & Romeljö, 2010) as well as with growing evidence suggesting greater severity of the addiction in women compared with men. In a review, Becker & Hu (2008) conclude that females begin regularly self-administering licit and illicit drugs of abuse at lower doses than do males, but use escalates more rapidly to addiction, and females are at greater risk for relapse following abstinence. In a previous study on Spanish heroin addicts in naltrexone maintenance treatment (Ochoa et al., 2008), the authors found that women had a poorer prognosis than men despite having fewer disruptive addiction behaviors (women showed less frequent cocaine use, less use of intravenous cocaine, lower frequency of alcohol and cannabis consumption, and shorter period of heroine abuse). On the other hand, Bauer et al. (2008) found a higher mortality rate among men and also found that women who survived scored significantly better in the categories concerning health problems, drug misuse, psychiatric and physical

![Fig. 1. Kaplan–Meier curve estimated for the heroin-dependent sample of patients against the curve that would be expected if the sample had been chosen randomly from the total Spanish population.](image-url)
status, and could be more successfully followed-up. Stenbacka et al. (2010) explain the difference in mortality by a lower mortality rate among women in general. Our results suggest that although heroin dependence is less prevalent in women than men, the severity of the addiction in terms of mortality is similar to that of men.

However, caution is needed in interpreting the p < 0.10 result for differences in mortality between genders, given the sample size. The same curve obtained with a larger sample, may have showed significant statistical differences in mortality rates. Differences from previous research could be due to a limited sample size in the current study.

4.2. Causes of death and HIV morbidity

Among the 106 confirmed deaths over the 25-year follow-up period, the most common cause of death (20.4%) was HIV/AIDS. We are not the only authors to highlight the high premature death rate in the opioid-dependent population, but our results disagree with the majority of follow-up studies where drug overdose is the most common cause (Bauer et al., 2008; Hser et al., 2001; Nehkant et al., 2005). Our results, though, may be biased by the considerable loss of data regarding causes of death (60.2% unknown). However, these results are in agreement with three previous follow-up studies in Spanish, Swiss, and Scandinavian populations where the authors found that HIV-related deaths are the most prevalent in MMT patient cohorts (Davstad, Stenbacka, Leifman, & Romelsjö, 2009; Rehm et al., 2005; Sanchez-Carbonell & Seus, 2000; Stenbacka et al., 2010). These results partially confirm the statement that MMT apparently reduces deaths related to overdose and needle-transmitted diseases (Kleber, 2008). Nevertheless, an SMR of 22.5 in our sample of MMT patients suggests that MMT cannot be counted as a huge success.

The impact of HIV infection on mortality in opioid-dependent samples has been a subject of study since the early nineties (Bauer et al., 2008; Brugal et al., 2005; Ortí et al., 1996; Perucci et al., 1991; Sanchez-Carbonell & Seus, 2000; Selwyn, Hartel, Wasserman, & Drucker, 1989). In our sample, the impact of MMT on HIV and hepatitis cannot be estimated due to the lack of information on HIV infection prior to the enrollment of this particular cohort in MMT. In fact, cases of HIV infection in Spain were diagnosed for the first time in 1981, and there were only 19 cases of HIV diagnosed in Spain during the enrollment period of the study cohort.

4.3. Current heroin use

The rate of current use of heroin in the survivors sample (22.6%) is similar to previous reports in long-term follow-up studies of heroin addicts such as the one by Hser et al. (2001), with 20.7% heroin users 33 years after being admitted to the California Civil Addict Program, and 20% in the 33-year follow-up study by Nehkant et al. (2005) in England.

This study also finds that women who survived were more likely to have stopped using heroin compared with men, as reported in other studies (Bauer et al., 2008; Darke et al., 2007).

It is encouraging that trend studies find that the proportion of patients still addicted is declining, despite the pessimistic views expressed by some (Goldstein & Herrera, 1995; Hser et al., 2001). However, there is no way of knowing whether the proportion of drug-

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**Table 3**

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Gender</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (81)</td>
<td>Women (22)</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>22.2% (18)</td>
<td>13.6% (3)</td>
</tr>
<tr>
<td>Overdose</td>
<td>8.6% (7)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Cancer</td>
<td>2.5% (2)</td>
<td>9.1% (2)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>3.7% (3)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td>2.5% (2)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Homicide</td>
<td>2.5% (2)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Accident</td>
<td>0% (0)</td>
<td>4.5% (1)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1.2% (1)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>56.8% (46)</td>
<td>72.7% (16)</td>
</tr>
</tbody>
</table>

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**Fig. 2.** Kaplan–Meier curve estimated for the heroin-dependent sample of patients by gender against the curve that would be expected if the sample had been chosen randomly from the total Spanish population.
related deaths represents a selection bias. The 25-year follow-up survivors may represent the patients in the initial sample with the least severe dependency and thus more likely to stop using heroin.

4.4. Attrition of the sample and non-availability of data

The extensive efforts to locate patients resulted in a location rate of 74.3% of the initial study sample. Therefore information was not obtained for 25.7% of the patients. This result constitutes a high location rate as compared with studies that are similar in terms of sample size and follow-up length, such as the one by Bauer et al. (2008) with a 45.4% loss to follow-up in 10 years, but is lower than in the studies by Hser et al. (2001) and Nehlant et al. (2005) with 10% and 16% loss to follow-up, respectively. However, a number of factors, including frequent change of address by the patient, a pattern that is well known in this target group, add an extra dimension of difficulty to follow-up studies in opioid-dependent samples (Bauer et al., 2008; Marrero et al., 2005).

4.5. Limitations

Limitations of the study have already been covered in the Discussion. The main limitation of the study is the large amount of missing data on causes of death. Other limitations include the lack of data on HIV and HVB status at the start of the follow-up period, as well as the lack of standardization of the ad-hoc protocol that was used.

5. Conclusion

This study confirms the high mortality of heroin addicts even after enrollment in MMT. Taken together, our results suggest a different risk of addictive behaviors by gender. Severity of the addiction in terms of mortality was similar in both genders but women who survived the 25-year follow-up were more likely to have stopped using heroin than men. Future research examining the factors that underlie sex differences may lead to the development of safe and effective sex-specific behavioral and pharmacological therapies for drug abuse. There is a need for future research in this area, as well as on how men and women differ in their responses to different treatment programs and methods. New studies on treatment effectiveness are needed in order to assess sex differences in response to different treatment strategies.

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None of the funding institutions had further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Contributors

L. Jimenez-Treviño, Pilar A. Saiz, Mª Paz García-Portilla, Eduardo Gutiérrez (†) and Julio Bobes designed the study and wrote the protocol. Luis Jimenez-Treviño and Pedro Marina managed the literature searches and summaries of previous related work. Patricia Burón, Mª José Casares and Eva Mª Díaz-Mesa participated in clinical evaluations, data collecting and data processing. Fernando Sánchez-Lasheras and Eva Mª Díaz-Mesa undertook the statistical analysis. Luis Jimenez-Treviño and Pilar A. Saiz wrote the first draft of the manuscript. All authors except Eduardo Gutiérrez (†) contributed to and approved the final manuscript. Eduardo Gutiérrez (†) died before reviewing the final manuscript.

Conflict of interest

Luis Jimenez-Treviño: No conflict declared
Pilar A. Saiz: No conflict declared
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Pedro Marina: No conflict declared
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References


